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J Clin Pharmacol 1999 Jan;39(1):47-54

Pharmacokinetics and tolerability of intravenous trecovirsen (GEM 91), an antisense phosphorothioate oligonucleotide, in HIV-positive subjects.

Sereni D, Tubiana R, Lascoux C, Katlama C, Taulera O, Bourque A, Cohen A, Dvorchik B, Martin RR, Tournerie C, Gouyette A, Schechter PJ

Service de Medecine Interne, Hopital Cochin, Paris, France.

Trecovirsen, a 25-mer antisense phosphorothioate oligonucleotide targeted at the gag site of the HIV gene, was administered to HIV-positive volunteers as an i.v. infusion. Single doses ranged from 0.1 to 2.5 mg/kg in an ascending escalation in cohorts of 6 to 12 subjects. Plasma trecovirsen concentrations and pharmacokinetic parameters could be assessed at doses > or = 0.3 mg/kg. Peak plasma concentrations and AUC values increased disproportionately with increasing dose while elimination half-life increased and plasma clearance decreased, indicating a saturable process over this dose range. The only significant adverse event observed was an isolated, transitory increase in activated partial thromboplastin time at doses > or = 2.0 mg/kg that was related to plasma trecovirsen concentrations and is attributed to the polyanionic character of the molecule. Thus, trecovirsen administration was well tolerated in single i.v. doses up to 2.5 mg/kg.

Publication Types:

- Clinical trial

PMID: 9987700, UI: 99142173

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Oncogene 1999 May 13;18(19):3056-62

Myb targeted therapeutics for the treatment of human malignancies.

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For the past several years, we have been engaged in developing a therapeutically effective strategy for disrupting gene function with reverse complementary, or so called 'antisense', oligodeoxynucleotides (ODN). This pursuit has focused on finding appropriate diseases in which to apply this approach, and suitable gene targets. Of the genes that we have targeted for disruption using the antisense ODN strategy (Clevenger et al., 1995; Gewirtz and Calabretta, 1988; Ratajczak et al., 1992c; Small et al., 1994) one that has been of particular interest, and one where therapeutically motivated disruptions are now in clinical trial, is the myb gene (reviewed in Lyon et al., 1994). These trials involve treatment of human leukemias. These diseases are a logical choice for developing oncogene targeted therapies because of easy access to tissues, and the abundance of knowledge about the cell and molecular biology of these diseases. Nevertheless, as will be touched on below, other malignancies have also been examined as models for Myb targeted therapy with some surprisingly encouraging results. Finally, while we have focused our efforts on the ODN strategy, I will allude briefly to other strategies for disrupting Myb function with therapeutic intent.

Publication Types:

- Review
- Review, tutorial

PMID: 10378701, UI: 99305046

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Gastroenterology 1998 Jun;114(6):1133-42

A placebo-controlled trial of ICAM-1 antisense oligonucleotide in the treatment of Crohn's disease.

Yacyshyn BR, Bowen-Yacyshyn MB, Jewell L, Tami JA, Bennett CF, Kisner DL, Shanahan WR Jr

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BACKGROUND & AIMS: Intercellular adhesion molecule 1 (ICAM-1) plays an important role in the trafficking and activation of leukocytes and is up-regulated in inflamed mucosa in Crohn's disease. ISIS 2302 is an antisense phosphorothioate oligodeoxynucleotide that inhibits ICAM-1 expression. The aim of this study was to obtain preliminary assessment of tolerability, pharmacology, and efficacy of ISIS 2302 in Crohn's disease. METHODS: Twenty patients with active, steroid-treated Crohn's disease were randomized (3:1, ISIS 2302 to placebo) to receive over 26 days 13 intravenous infusions of ISIS 2302 (0.5, 1, or 2 mg/kg) or saline placebo in a double-blinded study. The patients were followed up for 6 months. RESULTS: At the end of treatment. 47% (7 of 15) of ISIS 2302-treated and 20% (1 of 5) of the placebo-treated patients were in remission (Crohn's Disease Activity Index [CDAI] < 150). At the end of month 6, 5 of these 7 ISIS 2302-treated remitters were still in remission, and a 6th patient had a CDAI of 156. Corticosteroid usage was significantly lower ($P = 0.0001$) in the ISIS 2302-treated patients. These findings were corroborated by significant increases in beta7 and alpha d bearing CD3+ peripheral blood lymphocytes and by decreases in intestinal mucosal ICAM-1 expression during the treatment period. CONCLUSIONS: ISIS 2302 seems to be a well-tolerated and promising therapy for steroid-treated Crohn's disease.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 9609749, UI: 98282350

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J Hematother 1997 Oct;6(5):441-6

Ex vivo treatment of bone marrow with phosphorothioate oligonucleotide OL(1)p53 for autologous transplantation in acute myelogenous leukemia and myelodysplastic syndrome.

Bishop MR, Jackson JD, Tarantolo SR, O'Kane-Murphy B, Iversen PL, Bayever E, Joshi SM, Sharp JG, Pierson JL, Warkentin PI, Armitage JO, Kessinger A

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Effective ex vivo purging techniques can decrease the likelihood of infusing bone marrow contaminated with leukemic cells during autologous transplantation. In preliminary studies, OL(1) p53, a 20-mer phosphorothioate oligonucleotide directed against p53 mRNA, decreased the number of acute myelogenous leukemia (AML) cells in vitro, suggesting a possible role for OL(1)p53 in purging bone marrow harvests of leukemia cells. To demonstrate that OL(1)p53 was nontoxic to hematopoietic progenitor cells, normal bone marrow cells were incubated with 10 microM OL(1)p53 for 36 h, and hematopoietic progenitor cell survival was determined by in vitro colony assays. OL(1) p53 had no toxic effect on the growth of either myeloid (CFU-GM) or erythroid (BFU-E) progenitor cells. OL(1)p53 was then used to ex vivo purge bone marrow harvests from nine patients with either AML or myelodysplastic syndrome (MDS). Bone marrow cells were incubated with 10 microM OL (1)p53 for 36 h before transplantation. The median times posttransplantation for the patient to recover an absolute neutrophil count greater than 0.5 x 10(9)/L and a platelet transfusion independence were 30 days and 56 days, respectively. Incubation of bone marrow cells with OL(1)p53 had no detrimental effect on the growth of hematopoietic progenitor cells, and transplantation of autologous bone marrow cells treated with the phosphorothioate oligonucleotide, OL(1)p53, resulted in successful recovery of circulating neutrophils following high-dose therapy in patients with AML or MDS. The data show that OL(1)p53 can be used safely to purge autologous bone marrow harvests from patients with leukemia.

Publication Types:

- Clinical trial

PMID: 9368180, UI: 98034550

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Hum Gene Ther 1998 Nov 1;9(16):2407-25

A controlled, Phase 1 clinical trial to evaluate the safety and effects in HIV-1 infected humans of autologous lymphocytes transduced with a ribozyme that cleaves HIV-1 RNA.

Wong-Staal F, Poeschla EM, Looney DJ

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This Phase I study, "Ribozyme Gene Therapy of HIV-1 Infection" (UCSD HSC #971072, FDA BB-IND 6405), is a prospective, open-label trial of infusion of autologous gene-altered cells into asymptomatic HIV-1 seropositive individuals. The objectives of this trial are to test the safety, feasibility, and potential efficacy of T-cell ribozyme gene therapy of HIV-1 infection. To accomplish this, autologous CD8-depleted mononuclear cells are transduced with ribozyme expressing or control murine retroviral vectors, expanded ex vivo, and and infused. Subjects are monitored intensively to determine effects of infusion on HIV burden and replication. In addition, in vivo survival of control and ribozyme transduced cells is followed in an effort to obtain evidence of proof of concept. A unique strategy of sample blinding is introduced in this protocol, wherein both subject and control specimens are supplied to the research laboratory as coded samples, spiking blood from HIV seropositive volunteers matched for CD4 lymphocyte count with known but varying numbers of cells transduced with each vector. While this study is still in progress, preliminary results indicate that infusion of gene-altered, activated T-cells in HIV infected patients is safe, and that transduced cells can persist for long intervals in HIV-infected subjects. Results also suggest ribozyme transduced cells may possess a survival advantage in vivo.

PMID: 9829540, UI: 99045005